was sufficiently higher than that for topotecan therapy in previous studies [8,11]. The secondary endpoints, PFS and OS, were also favorable, and no treatment-related deaths occurred in this study. On the basis of these results, we conclude that AMR monotherapy is suitable as an effective and safe treatment option for refractory SCLC.

Jotte et al. [15] reported the results of a randomized phase III trial of AMR versus topotecan as second-line treatment for SCLC. The study randomized 637 patients in a 2:1 ratio for treatment with AMR ($n = 424$) or topotecan ($n = 213$). Treatment with AMR and topotecan showed similar OS periods (median, 7.5 *v* 7.8 months; hazard ratio for death, 0.880; 95% CI, 0.733–1.057; $P = 0.17$); however, higher ORRs (31.1% *v* 16.9%; $P = 0.0001$) and PFS periods (median, 4.1 *v* 3.5 months; hazard ratio for death or disease progression, 0.802; 95% CI, 0.667–0.965; $P = 0.0182$) were found with AMR therapy, and toxicity levels were more acceptable than those with topotecan therapy. Furthermore, in a subset analysis of 295 patients with refractory SCLC, AMR therapy demonstrated a modest improvement in OS (median, 6.2 *v* 5.7 months; hazard ratio for death, 0.766; 95% CI, 0.589–0.997; $P = 0.0469$). These results support our assertion that AMR monotherapy is a reasonable treatment option for patients with refractory SCLC.

In this study, a subgroup analysis revealed that prior treatment with etoposide, a topoisomerase II inhibitor, was associated with a poorer response to AMR and poor survival. Ettinger et al. [16] reported the results of a phase II study of AMR as a second-line therapy for patients with platinum-refractory SCLC. In total, 75 American and European patients were enrolled, of whom, 67 (89.3%) were pretreated with a chemotherapy regimen including etoposide. The confirmed ORR of AMR therapy was 21.3% (95% CI, 12.7–32.3%) and the median PFS was 3.2 months (95% CI, 2.4–4.0 months). These efficacy data are similar to those of the patients previously treated with etoposide in the present Japanese study. Therefore, previous chemotherapy with etoposide, but not ethnic differences, may have influenced the efficacy of AMR therapy. Preclinical studies [17–20] have suggested that treatment with topoisomerase I inhibitors results in downregulation of the topoisomerase I target and reciprocal upregulation of topoisomerase II, thereby causing hypersensitivity to topoisomerase II inhibitors. Conversely, treatment with topoisomerase II inhibitors results in downregulation of topoisomerase II and upregulation of topoisomerase I. These results may explain why prior treatment with etoposide was associated with a lower response to AMR therapy in the present study.

Although etoposide plus cisplatin (EP) is considered the standard first-line chemotherapy for patients with extensive-stage SCLC in Western countries, irinotecan, a topoisomerase I inhibitor, plus cisplatin (IP) is generally used for Japanese patients, which is based on the results of a previous phase III study comparing IP with EP for extensive-stage SCLC (JCOG9511) [2]. AMR may also play an important role in the treatment of refractory SCLC, especially for patients previously treated with IP. In a recent Japanese phase III study comparing AMR plus cisplatin (AP) with IP for the treatment of extensive-stage SCLC (JCOG0509) [21], similar PFS periods were found for AP and IP (median, 5.1 *v* 5.7 months), but AP was inferior to IP in terms of OS (median, 15.3 *v* 18.0 months). Over 90% patients in both groups received subsequent chemotherapy. The most commonly administered drugs after the termination of treatment were topotecan in the AP group and AMR in the IP group. Subsequent chemotherapy with AMR may have contributed to the longer OS period in the IP group.

The most common severe toxicity associated with AMR therapy in the present study was myelosuppression in the form of neutropenia. No treatment-related death was observed, which was probably because of the reasonable protocol-specified dose reductions and/or treatment delays. However, patients experienced febrile neutropenia more frequently in the present study (26.8%) than in previous studies (5.0–13.8%) [9,13,16]. According to the guidelines of the American Society of Clinical Oncology, prophylactic G-CSF use is clinically effective when the risk of febrile neutropenia is 20% [22]. To decrease the incidence of febrile neutropenia in patients treated with AMR for refractory SCLC, aggressive treatment of myelosuppression, including prophylactic G-CSF use, should be considered. Nonhematological toxicity was generally mild, but the treatment was terminated in eight patients (9.8%) because of unacceptable toxicity levels, including pneumonitis in seven. Although no death was associated with pneumonitis in the present study, careful monitoring for the development of pneumonitis is necessary. Similar to previous studies [9,13,16], no evidence of anthracycline-induced cardiotoxicity was found.

In conclusion, AMR monotherapy for refractory SCLC showed a favorable tumor response, prolonged survival, and acceptable toxicity, especially in patients not previously treated with etoposide. Therefore, AMR monotherapy presents a standard treatment option for refractory SCLC.

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Conflict of interest statement

The authors report no conflicts of interest that could inappropriately influence this work.

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A phase 2 study of bevacizumab in combination with carboplatin and paclitaxel in patients with non-squamous non-small-cell lung cancer harboring mutations of *epidermal growth factor receptor* (*EGFR*) after failing first-line EGFR-tyrosine kinase inhibitors (HANSHIN Oncology Group 0109)

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ABSTRACT

Objectives: We have conducted a phase 2 study to evaluate the efficacy and safety of carboplatin, paclitaxel, and bevacizumab in patients with non-squamous non-small-cell lung cancer (NSCLC) who are *epidermal growth factor receptor* (*EGFR*) mutation positive and for whom EGFR-tyrosine kinase inhibitor (TKI) 1st-line has failed.

Materials and methods: Patients with stage IIIB or IV non-squamous NSCLC harbored activating *EGFR* mutations that has failed 1st-line EGFR-TKI and an Eastern Cooperative Oncology Group performance status of 0 or 1 were included in this study. Patients received carboplatin at an area under the concentration–time curve 5 or 6, paclitaxel 200 mg/m^2, and bevacizumab 15 mg/kg on D1. The combination therapy was repeated every 21 days for up to three to six cycles. Bevacizumab was continued until disease progression or unacceptable toxicity for patients without disease progression (PD). The primary endpoint was objective response rate (ORR).

Results: Thirty-one patients were enrolled between March 2010 and January 2013, with 30 patients being eligible. ORR was 37% (90% CI; 24–52%) and disease control rate, 83% (95% CI; 66–92%). The median progression free survival (PFS) was 6.6 months (95% CI; 4.8–12.0 months) and median overall survival, 18.2 months (95% CI; 12.0–23.4 months). The most common grade ≥3 hematologic toxicity was neutropenia (93%), and non-hematologic toxicity, febrile neutropenia (20%). There were no clinically relevant grade ≥3 bleeding events and no treatment-related deaths.

Conclusion: The combination therapy of carboplatin, paclitaxel and bevacizumab did not achieve the initial treatment goal.

1. Introduction

Non-small-cell lung cancer (NSCLC) accounts for some 80–85% of lung cancer cases, with NSCLC prognostic factors being histology, age, performance status (PS), and gender. *Epidermal growth factor*

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receptor (*EGFR*) mutation has also been reported to be a prognostic factor and predictive factor in treatment [1–3]. I-CAMP, which conducted pooled analyses of gefitinib treatment in seven phase 2 studies for *EGFR* mutation-positive patients, indicated favorable clinical findings in terms of a response rate (RR) of 76.4%, median PFS of 9.7 months, and median overall survival (OS) of 24.3 months [4]. A Phase 3 study (IPASS) comparing doublet chemotherapy (carboplatin/paclitaxel) to gefitinib in Asians (never/mild smokers) indicated that EGFR mutation predicts EGFR-TKI benefits better than clinical background [5].

In recent years, there have been reports of phase 3 studies comparing cytotoxic chemotherapy and EGFR-TKI as 1st-line chemotherapy for *EGFR* gene mutation positive patients [6–9]. Regardless of the study, EGFR-TKIs have shown significantly longer PFS, establishing the utility of their 1st-line use. Nonetheless, none of the studies have indicated any significant difference in OS. Moreover, some of the studies reported that regimens using both cytotoxic chemotherapy and an EGFR-TKI improved prognosis the best. Accordingly, it may be important to use effective cytotoxic chemotherapy 2nd-line when an EGFR-TKI has been selected for use 1st-line. Unfortunately, it is yet unclear as to what the best 2nd-line regimen is for use subsequent progression after EGFR-TKI treatment or discontinuation of treatment due to adverse events.

Bevacizumab is a chimeric monoclonal antibody used on vascular endothelial growth factor (VEGF). A randomized placebo-controlled phase 3 study (Eastern Cooperative Oncology Group (ECOG) E4599 trial) with a primary endpoint of OS that examined the added effect of bevacizumab on carboplatin and paclitaxel showed a significantly longer median OS of 12.3 months in the carboplatin, paclitaxel, and bevacizumab group than the 10.3 months in the carboplatin and paclitaxel group (HR = 0.79, $p = 0.003$). Naumov et al. [10] have reported that bevacizumab may provide an antitumor effect on an EGFR-resistant NSCLC cell line harboring resistant *EGFR* mutation (T790M).

To summarize, while adding on bevacizumab to carboplatin and paclitaxel 2nd-line after administering an EGFR-TKI 1st-line for patients harboring an *EGFR* mutation promises an additional treatment effect, there have not been any reports of studies on post 2nd-line treatment on this type of patient group. As such, we have conducted a phase 2 study to evaluate the efficacy and safety of carboplatin, paclitaxel, and bevacizumab for non-squamous NSCLC patients who are *EGFR* mutation positive and failed on EGFR-TKI 1st-line, and examine whether it can be considered standard treatment or not.

2. Materials and methods

2.1. Patients eligibility

Eligible patients had histologically or cytologically confirmed non-squamous NSCLC, harbored activating *EGFR* mutations (either exon 19 deletion or L858R in exon 21), were confirmed to have PD after EGFR-TKIs 1st-line, were stage IIIB or IV (diagnosed according to the seventh edition of the Union for International Cancer Control staging system) or suffered a recurrence after surgery, and were aged ≥20 years. Patients were also required to have measurable legions as defined by the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1; an Eastern Cooperative Oncology Group (ECOG) PS of 0 or 1; life expectancy ≥3 months; adequate bone marrow, hepatic, and renal function. Key exclusion criteria were: a tumor invading major blood vessels or with cavitation; hemoptysis (≥2.5 mL per event); history of coagulation disorders or therapeutic anticoagulation; uncontrolled hypertension; an untreated ≥1 cm or symptomatic brain metastasis; interstitial pneumonia recognized on chest computed tomography (CT) scan; supporting radiation therapy occupying the pulmonary region in the 3 months before enrollment; or major surgery within 28 days before enrollment.

The protocol was approved through institutional ethical review boards each of the participating institutes, and all patients were provided written informed consent before treatment. The study was conducted in accordance with the ethical principles in the Declaration of Helsinki. The study has been registered under University hospital Medical Information Network (UMIN) Clinical Trials Registry Identifier, UMIN 000003263.

2.2. Study design and treatment

The study was designed as a prospective, multicenter, single-arm phase 2 study of 2nd-line combination therapy with paclitaxel, carboplatin, and bevacizumab followed by continuous maintenance therapy with bevacizumab. The primary endpoint was treatment efficacy measured as the ORR in patients who have received at least one cycle of the initial combination therapy. OS, PFS, the disease control ratio (DCR), and adverse events also were evaluated as secondary endpoints.

Patients received paclitaxel at a dose of 200 mg/m^2, carboplatin at a dose calculated to produce an area under the concentration–time curve of 5 or 6 mg per milliliter per minute, and bevacizumab at a dose of 15 mg/kg given intravenously on D1. The combination therapy was repeated every 21 days for up to three to six cycles unless there was evidence of PD or intolerance of the study treatment. After three to six cycles of combination therapy, patients who attained a complete response (CR), a partial response (PR), or stable disease (SD) continued to receive cycles of maintenance therapy with bevacizumab every 21 days until they had evidence of PD or unacceptable toxic effects developed. Subsequent cycles of treatment were withheld until the following criteria were satisfied: neutrophil count ≥1500/μL; platelet count ≥100,000/μL; PS 0–2; serum total bilirubin concentration ≥1.5 mg/dL; grade ≤2 weight loss, abnormal electrolytes, peripheral neuropathy, and hepatotoxicity (based on aspartate aminotransferase, alanine aminotransferase, and total bilirubin levels); grade ≤2 hypertension; grade ≤2 proteinuria; grade 0 hemoptysis or bleeding; and no infection with fever of at least 38 °C. The study therapy was stopped if grade ≥2 hemoptysis developed or if bleeding persisted after treatment of hemorrhage. Patients also were to be removed from the study if the next treatment cycle had not started within 42 days of the previous dosing as a result of toxicity. If the patient presented febrile neutropenia, thrombocyte count ≤25,000/μL, grade ≥3 non-hematologic toxicities, or grade ≥2 peripheral neuropathy, the doses of paclitaxel and carboplatin were modified in the subsequent cycles.

2.3. Baseline and treatment assessments

The baseline evaluations included medical history, physical examination, electrocardiogram, ECOG PS, and laboratory analyses. CT scans of the chest and the upper abdomen, and magnetic resonance imaging (MRI) studies or CT scans of the brain, and bone scintigraphy or positron emission tomography (PET)-CT studies were performed for tumor assessment within 28 days of initiation of the study treatment. Tumor measurements were assessed with chest X-ray, CT scans, MRI studies, or bone scintigraphy or PET-CT studies. CT scans were repeated with every 2 cycles until PD, MRI studies or CT scans of the brain were repeated with every 3 months or on the appearance of any neurologic symptoms, and bone scintigraphy or PET-CT studies were performed every 6 months or on the appearance of any bone-related symptoms. Objective tumor responses were based on the RECIST version 1.1. ORR was confirmed via extramural review. Toxicity evaluations

were based on the National Cancer Institute Common Toxicity Criteria (NCI-CTC) version 4.0.

2.4. Statistical analysis

In light of the previous data [11], we assumed that an RR of 60% in eligible patients would indicate potential usefulness, while a rate of 30% would be the lower limit of interest. Based on the assumption, the number of patients needed to provide the 90% power for a one-sided 0.05 level of type I error was calculated to be 23. Taking ineligible patients into account, the sample size was set at 30 in our study.

Efficacy and safety analyses were planned for patients who received at least one dose of the treatment. Objective RR and DCR rates were calculated, and their 95% confidence intervals (CIs) were estimated. PFS and OS were analyzed using Kaplan–Meier method to estimate the median points with 95% CIs. All statistical analyses were performed with SAS 9.3 for Windows (SAS Institute, Cary, NC).

3. Results

3.1. Patient characteristics

Thirty-one patients were enrolled between March 2010 and January 2013. One patient was excluded from safety and efficacy analyses because the patient was diagnosed with malignant lymphoma after the initiation of protocol treatment. As such, 30 patients (19 males and 11 females) with a median age of 64 (range 45–74) were evaluated for safety and efficacy. The median follow-up period was 18 months, and the baseline patient characteristics are shown in Table 1. Twenty-seven patients (90%) had adenocarcinoma histology, 27 patients (90%) had stage IV disease, and 18 patients (60%) were never-smokers. The breakdown of the *EGFR* mutation status showed that 19 patients (63%) had an exon 19 deletion and 11 patients (37%) had L858R point mutations in exon 21.

3.2. Treatment

The median number of induction chemotherapy cycles was 4 (range 1–5). After initial chemotherapy between 3 and 6 cycles, 20 patients (67%) received maintenance bevacizumab for a median of 2.5 cycles (range 1–42).

Table 1
Patient characteristics.

Characteristics	$n=30$
Median age, years (range)	64 (45–74)
Gender, *n* (%)	
Female	11 (37)
Male	19 (63)
ECOG PS, *n* (%)	
0	9 (30)
1	21 (70)
Smoking status, *n* (%)	
Never	18 (60)
Ever	12 (40)
Histology, *n* (%)	
Adenocarcinoma	27 (90)
NSCLC, NOS	3 (10)
Stage, *n* (%)	
IIIB	0 (0)
IV	27 (90)
Recurrence	3 (10)
EGFR mutation status, *n* (%)	
Exon19 del	19 (63)
Exon21 L858R	11 (37)

Table 2
Tumor response in evaluable patients according to RECIST.

	$n=30$
Objective response	
Complete response, *n* (%)	0 (0)
Partial response, *n* (%)	11 (37)
Stable disease, *n* (%)	14 (47)
Progressive disease, *n* (%)	2 (7)
Not evaluable, *n* (%)	3 (10)
Objective response rate (%)	37
95% CI, %	22–56
Disease control rate (%)	83
95% CI, %	66–92

3.3. Efficacy

ORR was 37% (90% CI; 24% to 52%) and DCR, 83% (95% CI; 66% to 92%) (Table 2). Maximum changes in tumor measurements are presented in Fig. 1. The median PFS was 6.6 months (95% CI;

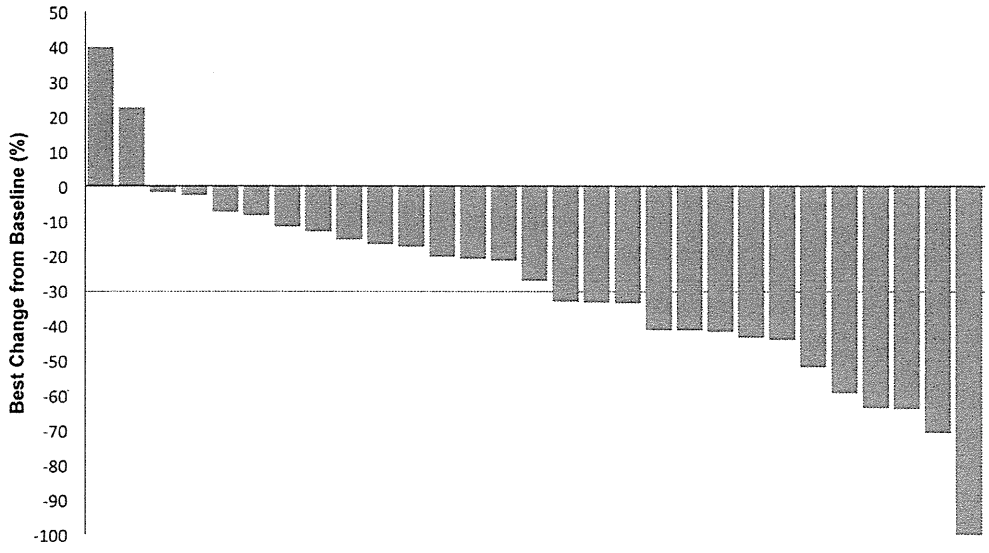

Fig. 1. Waterfall plot of best change from baseline.

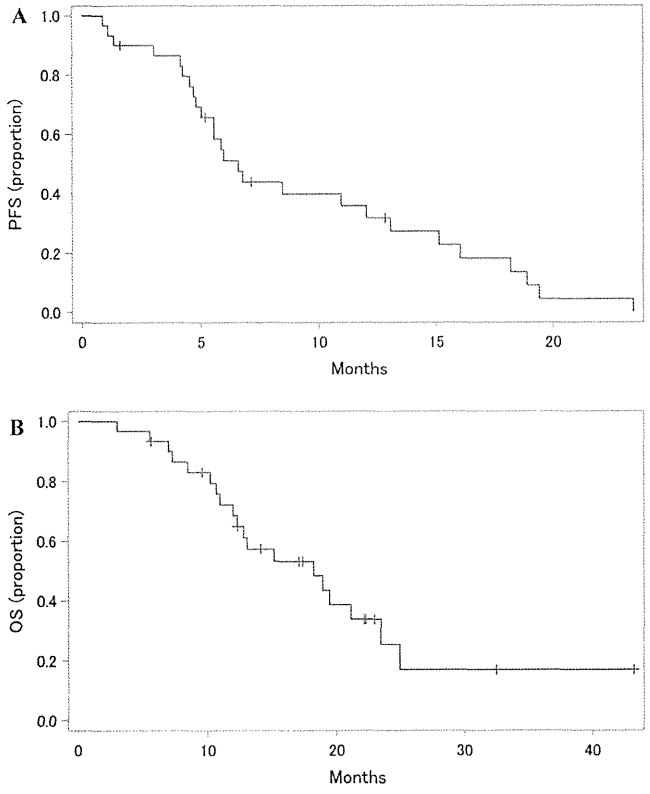

Fig. 2. (A) Kaplan–Meier curve for progression free survival. (B) Kaplan–Meier curve for overall survival.

4.8–12.0 months) (Fig. 2A) and median OS was 18.2 months (95% CI; 12.0–23.4 months) (Fig. 2B).

3.4. Toxicity

Thirty patients who received the study treatment were deemed eligible for safety analysis. The major adverse events are listed in Table 3. Grade ≥3 hematologic toxicities included neutropenia (93%), leukopenia (57%), anemia (14%), and thrombocytopenia (7%). Grade 3 or higher non-hematologic toxicities included hypertension (30%), febrile neutropenia (20%), fatigue (7%), dyspnea (3%), diarrhea (3%), ALT increased (3%), sensory neuropathy (3%), infection (3%), and infusion reaction (3%). There were no clinically relevant grade ≥3 bleeding events, and there were no treatment-related deaths.

3.5. Post-study treatment

Progression was observed in 25 of the 30 patients deemed to be eligible for treatment in the study, and 23 (76%) patients received post-study treatment (Table 4). The respective treatments received were cytotoxic chemotherapy in 15 patients (bevacizumab combination in 7 patients), bevacizumab alone in 3 patients and EGFR-TKIs in 5 patients.

4. Discussion

To date, there have been several controlled studies regarding the use of EGFR-TKIs and cytotoxic chemotherapy for *EGFR* gene mutation positive patients [12]. The findings from these studies show that there are no differences in OS regardless of the regimen used 1st-line. There has been a report, however, that prognosis was better in an arm in which platinum doublet was used after EGFR-TKI failure (whereby an EGFR-TKI has been used 1st-line) than in an arm in which it was not [13]. Accordingly, we conducted a prospective study on treatment with carboplatin/paclitaxel/bevacizumab after EGFR-TKI failure. There were no outcomes on treatment after 1st-line treatment failure with EGFR-TKI that could be used as a reference, so the target RR was established in reference to the 60.7% RR and 6.9-month PFS obtained in the outcomes on chemotherapy-naïve Japanese patients in the JO19907 trial [11].

The RR, which was the primary endpoint, was 37% (90% CI; 24–52%). Our study did not meet the primary endpoint. Moreover, the median PFS was 6.6 months (95% CI; 4.8–12.0 months). Though the RR and PFS were virtually the same as in the E4599 trial, the findings were somewhat inferior to those in the JO19907 trial. Our study focused on 2nd-line treatment after EGFR-TKI, so the patient characteristics could have differed from a chemotherapy-naïve population. This may have influenced our results, and it suggests that it may have been more difficult to identify tumor shrinkage to evaluate with RECIST after EGFR-TKI than in chemotherapy-naïve patients.

Table 3
Toxicity grades associated with chemotherapy (*n*=30).

	Grade 1/2	Grade 3	Grade 4
Hematologic toxicity, *n* (%)			
Leukopenia	13(43)	13(43)	4(14)
Neutropenia	2(7)	8(26)	20(67)
Anemia	23(77)	4(14)	0(0)
Thrombocytopenia	12(40)	1(3)	1(3)
Non-hematologic toxicity, *n* (%)			
AST increased	11(37)	0(0)	0(0)
ALT increased	15(50)	1(3)	0(0)
Fatigue	22(73)	2(7)	0(0)
Nausea	14(47)	0(0)	0(0)
Vomiting	9(30)	0(0)	0(0)
Constipation	17(57)	0(0)	0(0)
Diarrhea	7(23)	1(3)	0(0)
Mucositis/Stomatitis	5(17)	1(3)	0(0)
Sensory neuropathy	22(73)	1(3)	0(0)
Febrile neutropenia	0(0)	6(20)	0(0)
Infection	3(10)	1(3)	0(0)
Interstitial pneumonia	0(0)	0(0)	0(0)
Infusion reaction	1(3)	1(3)	0(0)
Dyspnea	0(0)	0(0)	1(3)
Bleeding	11(37)	0(0)	0(0)
Epistaxis	9(30)	0(0)	0(0)
Hypertension	21(70)	9(30)	0(0)
Proteinuria	13(43)	0(0)	0(0)

AST, aspartate aminotransferase; ALT, alanine aminotransferase.

Table 4
Post progression therapy.

	n=30
Cytotoxic chemotherapy	15
Pemetrexed	5
Docetaxel/bevacizumab	3
Cisplatin/pemetrexed	2
Carboplatin/paclitaxel/bevacizumab	1
Carboplatin/pemetrexed/bevacizumab	1
S-1/bevacuzumab	1
Paclitaxel/bevacizumab	1
Docetaxel	1
Bevacizumab alone	3
EGFR-TKIs	5
Gefitinib	3
Erlotinib	2
No chemotherapy	7
No disease progression	5
Radiation therapy alone	2

The median OS from initial EGFR-TKI treatment was 38.7 months (95% CI; 21.5–49.4 months) (data not shown). This compares equally to the 34.8 months (gefitinib arm) and 37.3 months (cisplatin/docetaxel arm) in the WJTOG3405 study [14] (which included a postoperative recurrence of at least 40%) and is longer than the 27.7 months (gefitinib arm) and 26.6 months (carboplatin/paclitaxel arm) in the NEJ002 study [13], conceivably indicating that our results were relatively favorable. Therefore, we thought that treatment with carboplatin, paclitaxel, and bevacizumab after EGFR-TKI failure can be a promising treatment option.

The adverse events (AEs) had all been commonly observed in clinical studies on bevacizumab to date, i.e., there were no new AEs observed in our study. In regard to hematologic toxicity, there were no significant differences between the incidence of grade ≥3 leukopenia, neutropenia, anemia, and thrombocytopenia and those reported in other studies to date such as the JO19907 trial. Meanwhile, in regard to non-hematologic toxicity, the incidence of febrile neutropenia (20%) was somewhat high. Each case, though, recovered with normal coping measures, as the febrile neutropenia did not prove to be a significant issue. Moreover, the incidence of grade 1 or 2 bleeding events was 37% and grade ≥3, 0%, indicating that the hemorrhaging was controllable. Combined with the fact that there were no treatment-related deaths, these findings suggest that there are no safety-related issues with the use of carboplatin, paclitaxel, and bevacizumab after EGFR-TKI failure.

The current National Comprehensive Cancer Network guidelines and The Japan Lung Cancer Society guidelines consider use of platinum-based combination therapy in cases of progression after use of EGFR-TKI 1st-line. There actually have yet to be any prospective reports, however, with ours being the first. The only report of a prospective study on cytotoxic chemotherapy after EGFR-TKI failure is that of a phase 2 study in which pemetrexed or docetaxel was administered [15]. Regardless of the arm, the RR was 20% and median OS, 8.5 months. There is yet no evidence to support the recommendation of any regimen. Our outcomes compare favorably with reports to date including the E4599 trial, suggesting the regimen as a possible platinum-based combination therapy option after EGFR-TKI failure. There are virtually no other reports of prospective studies on similar populations, though, so more prospective studies in the future would represent a preferable development.

Conflict of interest

Dr. Satouchi has received honoraria from Chugai Pharmaceutical and Nippon Kayaku. Dr. Hattori has received an honorarium from Chugai Pharmaceutical. Dr. Urata has received an honorarium from Chugai Pharmaceutical. Dr. Imamura has received an honorarium from Chugai Pharmaceutical. Prof. Morita has received honoraria from Chugai Pharmaceutical and Bristol Myers Squibb. Dr. Negoro has received an honorarium from Chugai Pharmaceutical. All other authors made no disclosure.

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JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Randomized Phase III Trial Comparing Weekly Docetaxel Plus Cisplatin Versus Docetaxel Monotherapy Every 3 Weeks in Elderly Patients With Advanced Non–Small-Cell Lung Cancer: The Intergroup Trial JCOG0803/WJOG4307L

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See accompanying editorial on page 534 and article on page 567

A B S T R A C T

Purpose
This phase III trial aimed to confirm the superiority of weekly docetaxel and cisplatin over docetaxel monotherapy in elderly patients with advanced non–small-cell lung cancer (NSCLC).

Patients and Methods
Chemotherapy-naïve patients with stage III, stage IV, or recurrent NSCLC age ≥ 70 years with a performance status of 0 or 1 who were considered unsuitable for bolus cisplatin administration were randomly assigned to receive docetaxel 60 mg/m^2 on day 1, every 3 weeks, or docetaxel 20 mg/m^2 plus cisplatin 25 mg/m^2 on days 1, 8, and 15, every 4 weeks. The primary end point was overall survival (OS).

Results
In the first interim analysis, OS of the doublet arm was inferior to that of the monotherapy arm (hazard ratio [HR], 1.56; 95% CI, 0.98 to 2.49), and the predictive probability that the doublet arm would be statistically superior to the monotherapy arm on final analysis was 0.996%, which led to early study termination. In total, 276 patients with a median age of 76 years (range, 70 to 87 years) were enrolled. At the updated analysis, the median survival time was 14.8 months for the monotherapy arm and 13.3 months for the doublet arm (HR, 1.18; 95% CI, 0.83 to 1.69). The rates of grade ≥ 3 neutropenia and febrile neutropenia were higher in the monotherapy arm, and those of anorexia and hyponatremia were higher in the doublet arm.

Conclusion
This study failed to demonstrate any survival advantage of weekly docetaxel plus cisplatin over docetaxel monotherapy as first-line chemotherapy for advanced NSCLC in elderly patients.

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INTRODUCTION

Lung cancer is the leading cause of cancer-related death in most developed countries. Non–small-cell lung cancer (NSCLC) accounts for 85% of all lung cancers, and more than 50% of patients with NSCLC already have advanced disease at diagnosis.[1] The number of elderly patients with lung cancer has also increased, and the median age at diagnosis is 70 years.[2]

The Elderly Lung Cancer Vinorelbine Italian Study, in which single-agent vinorelbine was compared with the best supportive care, first demonstrated the benefits of chemotherapy in elderly patients with advanced NSCLC.[3] In the Multicenter Italian Lung Cancer in the Elderly Study, a combination of vinorelbine plus gemcitabine did not improve survival over vinorelbine or gemcitabine alone and only increased the toxicity frequency.[4] Therefore, single-agent vinorelbine or gemcitabine was established as the standard treatment for elderly patients with NSCLC. We compared docetaxel (every 3 weeks) with vinorelbine in the West Japan Thoracic Oncology Group (the former name of the West Japan Oncology Group [WJOG]) 9904 study, which revealed significantly superior responses and better survival in the docetaxel arm.[5]

However, platinum-doublet chemotherapy has been recommended for patients with NSCLC with a performance status (PS) of 0 or 1,[6-8] and several retrospective subgroup analyses of large phase III trials have shown that the efficacy of platinum-doublet chemotherapy is similar in selected elderly patients and younger patients.[9,10] However, drug excretion or metabolic abilities generally decline because of age-related insufficiencies, especially in renal function. Therefore, modifications of anticancer drug dosages or schedules are recommended in chemotherapy for elderly patients with cancer.[11] In Japan, phase I[12] and II trials of weekly docetaxel plus cisplatin (DP) were conducted in elderly patients with NSCLC. The phase II study revealed a response rate (RR) of 52% (95% CI, 31% to 67%), a median survival time of 15.8 months, and no grade 4 toxicity.[13] On the basis of these promising results, we conducted a randomized phase III trial, the Japan Clinical Oncology Group (JCOG) 0207 trial, to compare DP with single-agent docetaxel. For the control arm, we chose weekly split docetaxel to investigate the effects of added cisplatin. In the second interim analysis, the overall survival (OS) seemed to be more favorable in the DP arm; however, an unexpected large difference was observed in the subgroup of patients age less than 75 years.[14] Therefore, considering the potential disadvantage of single-agent docetaxel therapy in this subgroup, we terminated the study and designed a new phase III trial in which the control arm received bolus infusions of docetaxel every 3 weeks, based on the West Japan Thoracic Oncology Group 9904 study.[5]

PATIENTS AND METHODS

Patients

Patients eligible for this study included chemotherapy-naïve patients with histologically or cytologically confirmed stage III (no indication for definitive radiotherapy), stage IV, or recurrent NSCLC who were age ≥ 70 years, with an Eastern Cooperative Oncology Group PS of 0 or 1 and adequate organ functioning, but who were unsuitable for bolus cisplatin administration. Considering that the age group of 70 to 74 years included those who were suitable and unsuitable for bolus cisplatin administration, we classified the reasons for administration unsuitability in this age group into six categories and examined patients for these conditions before enrollment. The pre-enrollment evaluation is described in the Appendix and Appendix Table A1 (online only). Prior radiotherapy, except for the primary lesion, was permitted if it had been completed at least 2 weeks before enrollment onto the study. Patients with symptomatic brain metastasis, active malignancy within the previous 5 years, superior vena cava syndrome, massive pleural effusion or ascites, critical vertebral metastasis, uncontrolled hypertension or diabetes, severe heart disease, active infection, hepatitis virus B surface antigen seropositivity, pulmonary fibrosis, polysorbate 80 hypersensitivity, or steroid dependence were excluded.

The study protocol was reviewed and approved by the JCOG Protocol Review Committee, WJOG executive board, and institutional review boards of each participating institution before study initiation. All patients provided written informed consent before enrollment.

Study Design and Treatment Plan

Eligible patients were randomly assigned to either the docetaxel arm (docetaxel 60 mg/m^2 infused over 60 minutes on day 1 every 3 weeks) or the DP arm (docetaxel 20 mg/m^2 infused over 60 minutes plus cisplatin 25 mg/m^2 infused over 15 to 20 minutes on days 1, 8, and 15 every 4 weeks). Patients were randomly assigned via the minimization method to balance the arms with the institution, disease stage (III v IV or recurrence), and age ($\geq v < 75$ years). In the DP arm, treatment was skipped under the following conditions: total leukocyte count less than 2,000/μL, platelet count less than 50,000/μL, creatinine level ≥ 1.5 mg/dL, and presence of fever or grade ≥ 3 nonhematologic toxicity (except constipation, weight loss, cough, hoarseness, and hyponatremia) on day 8 or 15. In both arms, subsequent cycle treatment was administered when the patients met the following conditions: total leukocyte count ≥ 3,000/μL, absolute neutrophil count ≥ 1,500/μL, platelet count ≥ 100,000/μL, serum creatinine level less than 1.5 mg/dL, total bilirubin level less than 2.0 mg/dL, ALT/AST ≤ 100 IU/L, and PS 0 to 2. Administration procedures, dose reduction criteria, and methods are detailed in the Appendix. Both treatments were repeated until the detection of disease progression or appearance of unacceptable toxicity. Radiographic tumor evaluations were performed and assessed, according to RECIST (version 1.0),[15] by each investigator at least every two cycles. Laboratory examinations were performed at least once a week in both arms, and toxicity was assessed before every cycle and classified in accordance with the National Cancer Institute Common Terminology Criteria for Adverse Events (version 3.0). Second-line treatment was administered at the investigator's discretion; however, cross-over to the other treatment arm was not permitted.

Quality-of-Life Assessment

Quality of life (QOL) was assessed by symptom scores, using the seven items of the Lung Cancer subscale of the Functional Assessment of Cancer Therapy–Lung.[16] The patients scored themselves immediately after providing informed consent and after completing the second and third treatment cycles. The proportions of patients with improved scores between the baseline and the end of the third cycle in each arm were compared. Missing data after treatment initiation were considered as indicating no improvement. In addition, we compared least squared means of the total scores from repeated measures analysis of variance with treatment arm, time, and their interaction and the 95% CI at each time point.

Supplementary Ad Hoc Analysis

Additional data collection and ad hoc analysis were performed. Data on the active epidermal growth factor receptor (*EGFR*) mutation status (exon 19 deletion or L858R point mutation) and poststudy treatments were collected because these were considered factors that could potentially affect survival.

Statistical Analysis

OS was the primary trial end point. The secondary end points included RRs, progression-free survival (PFS), symptom scores, and toxicities. The study was designed to provide results with a statistical power of 80%, using a one-sided $\alpha = .05$ to detect a 33% increase in median survival from 10 to 13.3 months. A total of 364 patients was required, accrued over a 4-year period with a 1-year follow-up period. Assuming a 5% rate of ineligible patients and patients lost to follow-up, the study sample size was set at 380 patients. OS, PFS, and responses were assessed in all eligible patients on an intent-to-treat basis. OS and PFS, which are defined in the Appendix, were estimated using the Kaplan-Meier method and were compared using the stratified log-rank test, according to age. Hazard ratios (HRs) of the treatment effects were estimated using the Cox proportional hazards model. RRs were compared using Fisher's exact test.

Two interim analyses were planned, the first after 50% of the patients were enrolled and the second after enrollment was completed. In these interim analyses, the primary end point, OS, was evaluated after adjustment for multiple comparisons, according to the Lan and DeMets method.[17] The O'Brien-Fleming–type α spending function was used. P values presented for the primary analysis were one-sided, in accordance with the trial design, whereas the other analysis values were two-sided. All analyses were performed using SAS software, release 9.1 (SAS Institute, Cary, NC). This study is registered with University Hospital Medical Information Network Clinical Trials Registry (www.umin.ac.jp/ctr/; identification No.: UMIN000001424).

RESULTS

The first interim analysis was performed in September 2010 and included data from 221 patients. Information time, defined as the

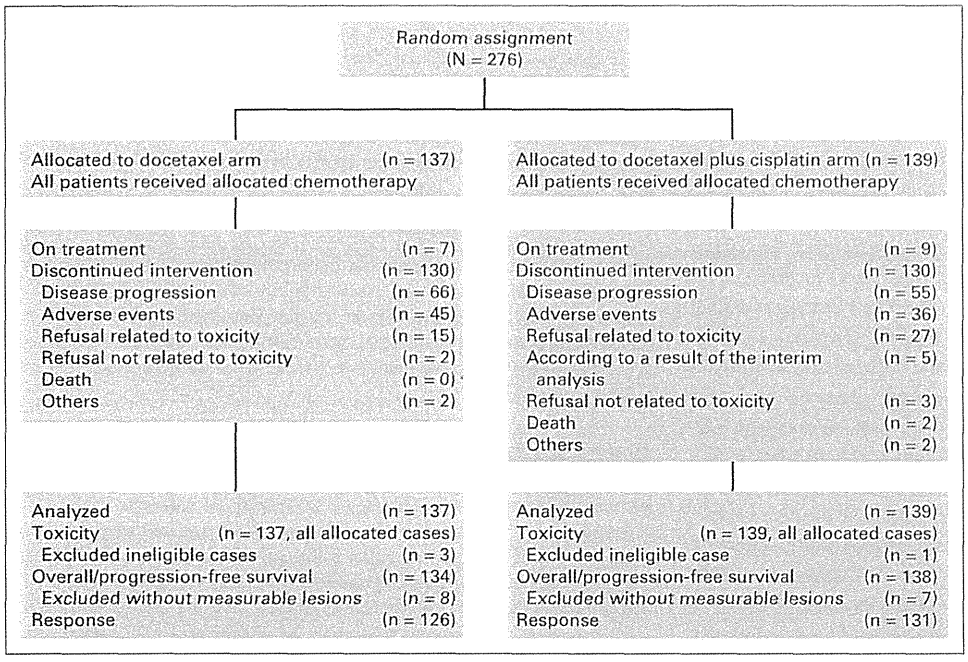

Fig 1. CONSORT diagram.

proportion of the interim events to the planned events, was 0.24 (73 of 304 events). Survival in the DP arm was inferior to that in the docetaxel arm (HR for DP to docetaxel arm, 1.56; 95% CI, 0.98 to 2.49; multiplicity-adjusted 99.99% CI, 0.62 to 3.88; one-sided $P = .97$ and two-sided $P = .06$ by stratified log-rank test), and the predictive probability that DP would be statistically superior to docetaxel on final analysis was 0.996% (< 1%). These results led to early study termination based on the recommendation of the Data and Safety Monitoring Committee, in accordance with the stopping guidelines prespecified in the protocol.

Patient Characteristics

Between October 2008 and September 2010, 276 patients (215 patients from JCOG and 61 patients from WJOG) were enrolled from 56 institutions (36 institutions affiliated with JCOG and 20 institutions affiliated with WJOG). Of these patients, 137 and 139 patients were assigned to the docetaxel and DP arms, respectively. All patients received the study treatments; therefore, all 276 patients were included in the safety analysis set. Three patients in the docetaxel arm and one patient in the DP arm were ineligible because of uncontrolled diabetes (ie, dependence on insulin injections) or previous malignancy. Therefore, these patients were excluded from survival analyses (Fig 1). Although the proportions of female patients and patients with adenocarcinoma were slightly higher in the docetaxel arm than in the DP arm, the patients' baseline characteristics were generally well balanced between the treatment arms (Table 1).

Treatment Delivery

The median number of treatment cycles was four (range, one to 18 cycles) in the docetaxel arm and three (range, one to six cycles) in the DP arm, and the proportion of patients in whom treatment continued for five or more cycles was higher in the docetaxel arm than in the DP arm (31% *v* 8%, respectively). In the docetaxel and DP arms, 37% and 4% of patients required one-step dose reductions, respectively. Furthermore, 19% of patients required two-step dose reductions in the docetaxel arm. In the DP arm, 19% of patients had one or more skipped treatments on day 8 or 15. The major reasons for

Table 1. Patient Demographics and Clinical Characteristics

Demographic or Clinical Characteristic	Docetaxel (n = 137)		Docetaxel/Cisplatin (n = 139)	
	No. of Patients	%	No. of Patients	%
Age, years				
Median	76		76	
Range	70-87		70-86	
< 75	31	23	32	23
≥ 75	106	77	107	77
Sex				
Male	95	69	101	73
Female	42	31	38	27
Smoking status*				
Never	38	28	36	26
Smoker	98	72	101	74
ECOG PS				
0	50	36	48	35
1	87	64	91	65
Stage				
III	42	31	43	31
IV or recurrence	95	69	96	69
Histology*				
Adenocarcinoma	91	67	86	63
Squamous	32	24	39	28
Others	13	10	12	9

Abbreviation: ECOG PS, Eastern Cooperative Oncology Group performance status.
*Data for one patient in the docetaxel monotherapy arm and two patients in the docetaxel plus cisplatin arm were missing.

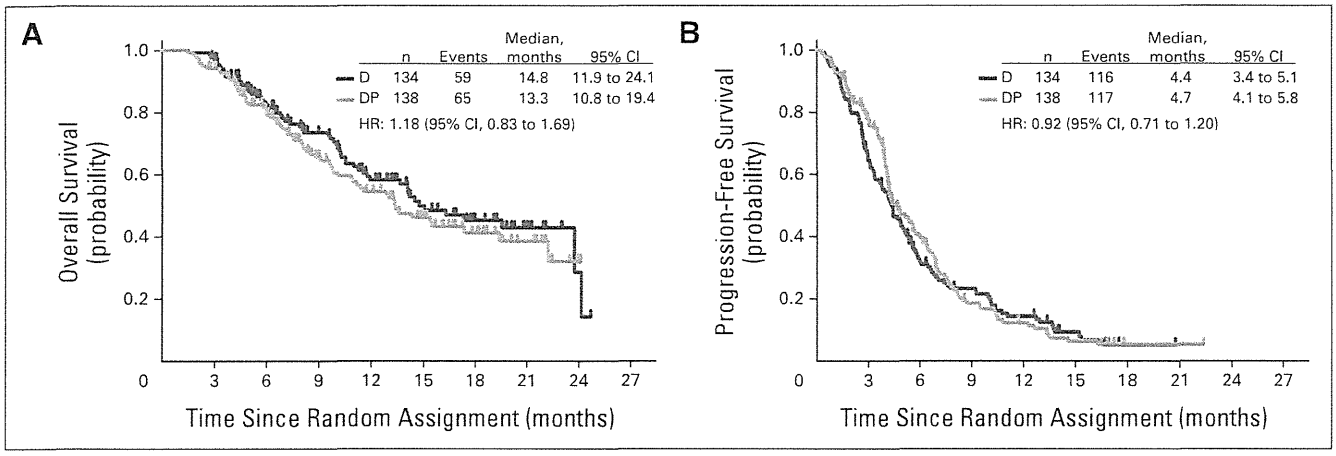

Fig 2. Kaplan-Meier curves for (A) overall survival and (B) progression-free survival. Tick marks indicate censored patients at the data cutoff point (November 2010). D, docetaxel; DP, docetaxel plus cisplatin; HR, hazard ratio.

treatment discontinuation in the docetaxel versus DP arms were disease progression (51% *v* 42%, respectively), adverse events (35% *v* 28%, respectively), and patient refusal to continue treatment as a result of toxicity (12% *v* 21%, respectively).

Efficacy

The overall RRs were 24.6% in the docetaxel arm (95% CI, 17.4% to 33.1%) and 34.4% in the DP arm (95% CI, 26.3% to 43.2%). The difference was not statistically significant ($P = .10$).

By November 22, 2010, 124 (45.6%) of the 272 eligible patients had died (docetaxel arm, n = 59; DP arm, n = 65). The median follow-up time for all eligible patients was 9.6 months. The 1-year survival rates were 58.2% and 54.5% in the docetaxel and DP arms, respectively. The HR for OS was 1.18 (95% CI, 0.83 to 1.69; Fig 2A). The HR for PFS was 0.92 (95% CI, 0.71 to 1.20; Fig 2B).

Toxicity

Hematologic and nonhematologic toxicities are listed in Table 2. Grade ≥ 3 leukopenia and neutropenia occurred more frequently in the docetaxel arm. The incidence of grade 4 neutropenia was 67.9% in the docetaxel arm but only 0.8% in the DP arm. Febrile neutropenia was observed only in the docetaxel arm at an incidence of 15.2%. Grade ≥ 3 anemia, hyponatremia, and anorexia were observed in more than 10% of patients in the DP arm. Four treatment-related deaths occurred, all in the DP arm (2.9%), including three patients who died of pneumonitis and one patient who died of unclassified sudden death.

QOL

Symptom score questionnaire responses were collected from 271 (98.2%) of 276 patients at baseline, 258 patients (93.5%) after the second cycle, and 247 patients (89.5%) after the third cycle. The

Table 2. Toxicities

	Docetaxel (n = 137)			Docetaxel/Cisplatin (n = 139)		
Adverse Event	Grade 3 or 4 (%)	Grade 4 (%)	Missing (No.)	Grade 3 or 4 (%)	Grade 4 (%)	Missing (No.)
Hematologic*						
Leukopenia	62.7	8.2	3	5.4	0	10
Neutropenia	88.8	67.9	3	10.1	0.8	10
Anemia	3.7	0.7	3	16.3	0.8	10
Thrombocytopenia	0	0	3	0.8	0	10
Nonhematologic*						
Febrile neutropenia	15.2	0	5	0	0	8
Hyponatremia	5.2	0.7	3	14.7	0.8	10
Hypoalbuminemia	1.5	—	6	4.7	—	10
Infection	7.6	0	5	8.4	0.8	8
Anorexia	1.5	0	5	10.7	0	8
Nausea	0.8	0	5	3.8	0	8
Diarrhea	3.8	0	5	0.8	0	9
Fatigue	3.0	0	5	5.3	0	8
Pneumonitis	5.3	0	5	2.3	0.8	8

NOTE. There were four treatment-related deaths (2.9%), all in the docetaxel plus cisplatin arm, including three deaths resulting from pneumonitis and one unclassified sudden death.
*Each value was calculated while excluding patients with missing data.

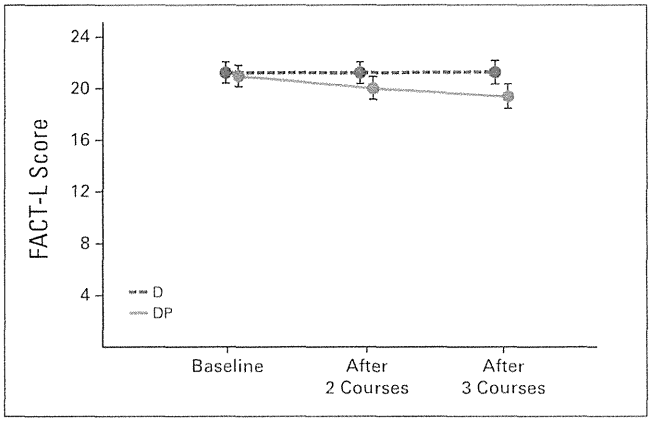

Fig 3. Quality-of-life assessments according to the seven-item Functional Assessment of Cancer Therapy–Lung (FACT-L). Dots and error bars indicate the least squared mean total scores and 95% CI, respectively. Higher scores indicate a better quality of life. D, docetaxel; DP, docetaxel plus cisplatin.

numbers of patients with missing data because of death or severe deterioration of the patient's general condition in the docetaxel and DP arms were one and six patients, respectively, after the second cycle and six and nine patients, respectively, after the third cycle. In the docetaxel and DP arms, 39.3% (53 of 135 patients) and 36.8% (50 of 136 patients) of patients had scores that improved from baseline to the end of the third cycle, which did not constitute a significant difference. Although the mean total score remained near its baseline value in the docetaxel arm, it declined gradually in the DP arm, changing in a statistically significant manner between baseline and cycle 3 ($P < .01$; Fig 3).

Supplementary Ad Hoc Analysis

Data forms were collected from 275 patients (except one patient from the docetaxel arm). *EGFR* mutation testing was performed in 79 patients (58%) and 74 patients (53%) in the docetaxel and DP arms, respectively; the results revealed active *EGFR* mutations in 22 patients in the docetaxel arm (16% overall and 28% of those tested) and 16 patients in the DP arm (12% overall and 22% of those tested). After protocol treatment completion, further drug treatment was administered to 74 patients (54%) in the docetaxel arm and 70 patients (50%) in the DP arm. During this treatment, EGFR tyrosine kinase inhibitor was administered to 35 patients (26%) and 23 patients (17%) in the docetaxel and DP arms, respectively.

Figure 4 shows the survival HRs according to subgroup analyses of the baseline and ad hoc characteristics. No significant differences between the two treatment groups were observed in any subgroup.

DISCUSSION

The standard treatment for fit patients with advanced NSCLC is platinum-doublet chemotherapy.[6,7] Several retrospective subgroup analyses have shown that platinum-doublet chemotherapy is similarly effective in elderly and younger patients and is well tolerated despite an increased incidence of toxicity.[9,10] These retrospective analyses, however, were performed in highly selected elderly populations. Generally, elderly patients are often unsuitable candidates for bolus cisplatin administration because of comorbid illnesses and/or organ dysfunction. Therefore, we considered it important to conduct a prospective investigation to determine whether the addition of a modified platinum agent might improve survival in elderly patients with NSCLC.

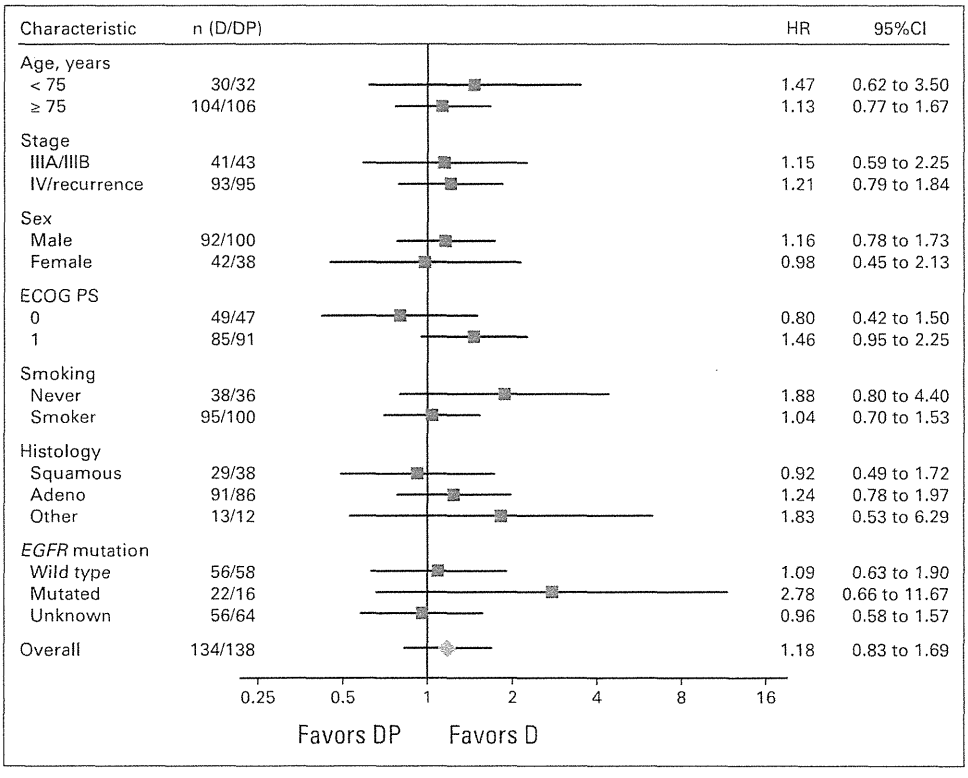

Fig 4. Subgroup analysis of overall survival. D, docetaxel; DP, docetaxel plus cisplatin; ECOG PS, Eastern Cooperative Oncology Group performance status; HR, hazard ratio.

In the phase II and previous phase III trials, we demonstrated that weekly split docetaxel and additional cisplatin reduced myelotoxicity and increased RRs.[13,14] In this study, we analyzed the add-on effect of weekly cisplatin over docetaxel monotherapy. Although the DP arm tended to have higher RRs than the docetaxel arm, this was reflected in neither the PFS nor the OS.

Although we collected information on comorbid illnesses, we did not assess the Charlson comorbidity index. Comprehensive geriatric assessments, including basic activities of daily living (ADLs), instrumental ADLs, Mini-Mental State Examination, and Geriatric Depression Scale evaluation, were also conducted for exploratory purposes. Although the prognostic values of these assessments have not been validated for elderly patients with lung cancer, it was suggested that ADLs and Mini-Mental State Examination can be useful.[18] In future research, we should evaluate these factors prospectively.

The proportions of female patients and patients with adenocarcinoma were slightly higher in the docetaxel arm than in the DP arm. In eastern Asia, including Japan, active *EGFR* mutations are often observed in such patients and have been reported as a favorable prognostic factor in patients with NSCLC.[19,20] According to a subgroup analysis, the median survival time was 12.8 months in the 114 patients (in the docetaxel plus DP arms) without *EGFR* mutation and 24.1 months in the 38 mutation-positive patients. The proportion of patients with active *EGFR* mutations was slightly higher in the docetaxel arm than in the DP arm. However, it would have been difficult to demonstrate the superiority of the DP arm in OS, considering the slight difference in PFS, even if there were no such imbalances.

In the docetaxel arm, a higher proportion of patients required dose reductions, yet these appropriate reductions lengthened treatment. In contrast, the DP arm included fewer patients who were able to continue treatment, despite the lower proportion of dose reductions and skipped treatments. We believe that declining QOL was an important cause of treatment discontinuation in the DP arm.

The toxicity profiles also differed between the two arms. In the docetaxel arm, neutropenia was most prominent, and grade 4 neutropenia occurred in up to 68% of the patients. Consequently, febrile neutropenia was observed in 15% of the patients in the docetaxel arm, whereas no patients experienced febrile neutropenia in the DP arm. The frequency of febrile neutropenia in the docetaxel arm was similar to that seen in a previous Japanese docetaxel study for elderly patients.[5] However, because febrile neutropenia was successfully managed with appropriate supportive treatments, there were no treatment-related deaths in the docetaxel arm. However, the DP arm had higher incidences of grade ≥ 3 anemia, hyponatremia, and anorexia. We suppose that these were the main causes of the decline in the QOL score in the DP arm. The median number of treatment cycles and the proportion of patients in whom treatment could be continued for five or more cycles in the DP arm were smaller than those in the docetaxel arm. These findings could be associated with the decline in QOL and might have affected OS in the DP arm. Three of four treatment-related deaths in the DP arm were caused by pneumonitis. It was reported that weekly docetaxel administration increases the frequency of pneumonitis.[21,22] In this study, there were few differences in the frequencies of pneumonitis between the two arms; however, more severe pneumonitis was observed in the DP arm.

Quoix et al[18] demonstrated the superiority of carboplatin plus weekly paclitaxel over conventional standard therapy, namely vinorelbine or gemcitabine monotherapy, in the Intergroupe Francophone de Cancerologie Thoracique 0501 study. The usefulness of platinum-based treatments in elderly patients was first shown in a prospective study. For elderly patients with NSCLC, carboplatin combination therapy may be preferable to a split cisplatin combination. However, the high incidence of toxicity could not be ignored, because treatment-related deaths occurred in 4.4% of patients in the doublet arm but only in 1.3% of patients in the monotherapy arm.[18] In contrast, a phase I trial of combined carboplatin plus pemetrexed (PEM), followed by maintenance PEM, showed good tolerability in elderly patients with nonsquamous NSCLC.[23] We consider that the combination of carboplatin plus PEM should be compared with docetaxel monotherapy.

In conclusion, this study failed to demonstrate any advantages of weekly DP over docetaxel monotherapy as first-line chemotherapy for elderly patients with advanced NSCLC, and docetaxel every 3 weeks remains the standard treatment for elderly patients with advanced NSCLC.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(s) and/or an author's immediate family member(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

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GLOSSARY TERMS

cisplatin: an inorganic platinum agent (cis-diamminedichloroplatinum) with antineoplastic activity. Cisplatin forms highly reactive, charged, platinum complexes, which bind to nucleophilic groups such as GC-rich sites in DNA, inducing intrastrand and interstrand DNA cross-links as well as DNA-protein cross-links. These cross-links result in apoptosis and cell growth inhibition. Carboplatin and oxaliplatin are other members of this class.

docetaxel: a member of the taxane group of antimitotic chemotherapy medications whose mode of action is to bind and stabilize microtubules and thus disrupt cell division.

non–small-cell lung cancer (NSCLC): a type of lung cancer that includes squamous cell carcinoma, adenocarcinoma, and large-cell carcinoma.

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Appendix

Reasons for Bolus Cisplatin Administration Unsuitability

Patients age 70 to 74 years were examined before enrollment for the following six conditions, which defined them as unsuitable for bolus cisplatin administration (Appendix Table A1): a combination of more than one mild organ dysfunction, but violating none of the inclusion criteria; a combination of comorbid illness and mild organ dysfunction, but violating none of the inclusion criteria; organ dysfunction not specified by the inclusion/exclusion criteria; a combination of more than one comorbid illness; a comorbid illness not specified by the exclusion criteria; or any other condition.

Procedures of Administration

In the docetaxel monotherapy arm, docetaxel was diluted with 250 to 500 mL of 5% glucose solution or physiologic saline and administered by intravenous infusion over 60 minutes.

In the docetaxel plus cisplatin (DP) arm, docetaxel was diluted with 250 mL of 5% glucose solution or 200 mL of physiologic saline and administered by intravenous infusion over 60 minutes. Cisplatin was administered by intravenous infusion over 15 to 20 minutes, directly or after being diluted with physiologic saline, after docetaxel administration. A total of 1,000 to 1,500 mL of fluid was administered before and after the administration of cisplatin. During treatment with cisplatin, careful attention was paid to urinary output, and diuretics such as mannitol and furosemide were administered if necessary. Antiemetics such as 5-hydroxytryptamine-3 receptor antagonists and steroids were also administered if necessary.

Dose Reduction Criteria and Methods

In both arms, the presence of grade 4 neutropenia, febrile neutropenia, or grade $\geq$ 3 nonhematologic toxicity (except anorexia, nausea, vomiting, hyponatremia, constipation, and hyperglycemia) necessitated dose reduction (docetaxel arm levels -1 and -2: docetaxel 50 and 40 mg/m^2, respectively; DP arm level -1: docetaxel 15 mg/m^2 and cisplatin 20 mg/m^2). In addition, if serum creatinine levels exceeded 2.0 mg/dL, the administration of cisplatin was stopped in subsequent cycles in the DP arm. The persistence of these toxicities after two dose-reduction steps in the docetaxel arm or one dose-reduction step of each drug in the DP arm prompted treatment discontinuation.

Definition of Overall and Progression-Free Survival

Overall survival was measured from the date of random assignment to death from any cause and was censored at the last follow-up date. Progression-free survival was measured from the date of random assignment to the first observation of disease progression or death from any cause if there was no progression. If there was no progression and the patient did not die, progression-free survival data were censored at the date on which the absence of progression was confirmed.

Table A1. Conditions Defining Patients As Unsuitable for Bolus Cisplatin Administration

Condition	No. of Patients	
	Docetaxel (n = 31)	Docetaxel/Cisplatin (n = 32)
Combination of more than one mild organ dysfunction, but violating none of the inclusion criteria	6	4
Combination of comorbid illness and mild organ dysfunction, but violating none of the inclusion criteria	5	8
Organ dysfunction not specified by the inclusion/exclusion criteria	8	3
Combination of more than one comorbid illness	1	7
Comorbid illness not specified by the exclusion criteria	2	2
Any other condition	9	8

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Original Article

Randomized controlled trial comparing docetaxel–cisplatin combination with weekly docetaxel alone in elderly patients with advanced non-small-cell lung cancer: Japan Clinical Oncology Group (JCOG) 0207†

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Abstract

Objective: Prospective trials specifically designed for elderly patients with advanced non-small-cell lung cancer demonstrating the benefit of platinum-based therapies are still lacking. This trial was designed to clarify whether the addition of cisplatin to monotherapy could improve survival for elderly patients.

Methods: Elderly patients (age ≥70 years, ECOG performance Status 0–1) with advanced non-small-cell lung cancer were randomized to receive docetaxel 20 mg/m^2 plus cisplatin 25 mg/m^2 on Day 1, 8 and 15 (docetaxel plus cisplatin) or docetaxel 25 mg/m^2 on the same schedule (docetaxel). Both regimens were repeated every 4 weeks until disease progression.

Results: One hundred and twenty-six patients were enrolled. Sixty-three were randomly assigned docetaxel plus cisplatin and 63 docetaxel monotherapy. Median age was 76 years (range 70–88). The second planned interim analysis was performed on 112 assessable patients (docetaxel/docetaxel plus cisplatin: 56/56). Although the formal criterion for stopping the trial was not met, the Data and Safety Monitoring Committee recommended study termination on ethical grounds based on the interaction (two-sided $P = 0.077$, hazard ratios for ≤74/≥75: 0.23/0.72) between age and subgroup and treatment arm, which suggested that docetaxel may not represent an adequate control arm regimen for the age subgroup of 70–74 years.

Conclusions: The interpretation of study results is limited due to early stopping. Further study is needed to confirm survival benefit of platinum-based chemotherapy for elderly non-small-cell lung cancer [UMIN-CTR (www.umin.ac.jp/ctr/) ID: C000000146].

Key words: cisplatin, docetaxel, elderly, non-small-cell lung cancer, interim analysis

Introduction

Non-small-cell lung cancer (NSCLC) remains the leading cause of cancer-related death in most developed countries (1). The rapid expansion of the elderly population in the majority of industrialized nations has resulted in a significant increase in the number of older patients diagnosed with NSCLC. Platinum-based doublet chemotherapy is considered the standard of care for fit patients with advanced NSCLC (2). Retrospective subset analyses of the trials involving young and elderly patients with no upper age limit have reported that elderly NSCLC patients with good performance status tolerate platinum-based combination chemotherapy well and achieve survival benefits similar to those of younger patients (3–6). However, elderly patients are under-represented in these clinical trials, making it difficult to extrapolate these results to elderly population, in general (7,8). Aging is associated with a number of physiological changes, such as deterioration of renal and liver function and decreased bone marrow reserves, which affect the tolerability and outcomes of cytotoxic chemotherapy (9,10). In addition, the presence of comorbid illnesses needs to be considered when caring for elderly patients (11). The 2004 American Society of Clinical Oncology guidelines recommended use of vinorelbine or gemcitabine monotherapy for elderly patients with advanced NSCLC (12) based on evidence from two Phase III trials specific for elderly patients (13,14). In addition, a Japanese Phase III study evaluating the role of docetaxel (D) monotherapy for elderly advanced NSCLC had demonstrated equivalence, if not superiority, for D to vinorelbine (15). In an effort to develop more effective treatments, the role of platinum-doublet has been evaluated employing attenuated platinum doses or carboplatin instead of cisplatin to achieve feasible therapeutic indices in elderly patients (16–18). A Japanese Phase II study evaluating the combination of weekly D and cisplatin in 33 patients ≥75 years old resulted in a response rate of 52%, median survival of 15.8 months, and an acceptable toxicity profile (19). This promising result led us to plan the current randomized Phase III study. We selected D, an agent used in the above-mentioned Phase II study (19), instead of vinorelbine or gemcitabine, as a control arm in order to evaluate clearly whether the addition of cisplatin to single-agent chemotherapy could improve survival for elderly patients.

Patients and methods

Study design

Patients who met all eligibility criteria were randomly allocated to receive one of the two regimens in equal proportion, as follows: arm A, D 25 mg/m^2 infused over 60 min on Days 1, 8 and 15; and arm B, D 20 mg/m^2 infused over 60 min plus cisplatin 25 mg/m^2 infused over 15–20 min on Days 1, 8 and 15.

Registration was made by telephone or fax to the Japan Clinical Oncology Group (JCOG) Data Center. Patients were randomized by the minimization method balancing the arms with institution, stage of disease (III versus IV) and age (≥75 versus ≤74 years). Treatment cycles for both treatment arms were repeated every 4 weeks until unacceptable toxicity or disease progression. Guidelines for dose adjustments were provided for chemotherapy-related toxicity. Dexamethasone and 5-HT_3 antagonist as antiemetic agents and 1000–1500 ml fluid infusion were recommended for patients assigned DP. No other chemotherapy, radiotherapy or experimental medication was permitted while the patient was under study and appropriate supportive care was provided. Radiographic tumor evaluation was carried out at least every two cycles and toxicity was assessed before every cycle.

Patient selection

Patients with histologically or cytologically confirmed diagnosis of Stage IIIA/IIIB (ineligible for definitive radiotherapy) or Stage IV NSCLC were enrolled in this study. All patients were required to be ≥70 years old with an ECOG performance status of 0 or 1, and adequate hematological, renal (serum creatinine ≤1.2 mg/dl) hepatic and respiratory functions. Previous surgery was allowed if it had been completed at least 4 weeks before inclusion. No prior radiotherapy for primary lesion was allowed. Patients eligible for 1 day bolus administration of cisplatin after considering renal and cardiac function and comorbid illnesses, or patients receiving prior chemotherapy were excluded from participation. This study protocol was reviewed and approved by the Protocol Review Committee of JCOG and the institutional review board at each participating institutions prior to initiation of the study, and the study was conducted in accordance with the precepts established in the Declaration of Helsinki. Patients who were eligible for participation provided written informed consent before undergoing any study procedure.

Statistical analysis

The trial was designed as a multicenter, prospective, randomized Phase III study. The primary endpoint for this trial was overall survival (OS). Secondary endpoints included response rates, progression-free survival (PFS), symptom score and toxicity.

The primary objective was to determine whether addition of cisplatin to monotherapy could improve survival for elderly patients with NSCLC. The study was designed with an 80% power using a one-sided alpha of 0.025 to detect a 50% increase in median survival from 7 months with D to 10.5 months with docetaxel plus cisplatin (DP). As a result, 220 patients (110 patients per arm) accrued in a 3-year period with a 1-year follow-up were required (20). Assuming a proportion of ineligible and lost to follow-up of 5%, sample size for the study was set at 230 patients. OS, PFS and response were assessed using the total eligible population. OS was measured from the date of randomization to the date of death from any cause and censored at the last follow-up date. PFS was measured from the date of randomization to the date of the first observation of disease progression, or the date of death from any cause if no progression had been identified. If there was no progression and if the patient had not died, data on PFS were censored as of the date on which the absence of progression was confirmed. Survival and PFS curves were estimated using the Kaplan–Meier method and compared using the stratified log-rank

test with age and stage as stratification factors. Hazard ratios of treatment effect were estimated using Cox proportional hazard modeling.

The first interim analysis was planned to confirm that response rate for the control arm was sufficiently high. Second and third interim analyses were planned for the primary endpoint of OS with adjustment for multiple comparisons taken into account according to the method of Lan and DeMets (21). The O'Brien Fleming-type alpha spending function was used. The second interim analysis was planned for the date on which half of the planned number of patients had been enrolled, and the third interim analysis was planned after the date on which all patients had been enrolled.

Response evaluation was performed according to Response Evaluation Criteria In Solid Tumors (22). Safety of the treatment regimens was assessed by calculating the percentage of patients experiencing Grade 3 or 4 toxicity using National Cancer Institute Common Toxicity Criteria version 2.0. Symptom score was assessed with the seven-item disease-specific subscale in the FACT-L (Functional Assessment of Cancer Therapy-Lung) (23) by patients themselves before treatment and 8 weeks later. The sum of the scores for all seven items was compared between the baseline and post-treatment assessments. The maximum attainable score was 28, with which the patient was considered to be asymptomatic. We calculated the difference between the baseline and post-treatment scores in each patient and compared them across treatment groups by analysis of covariance (ANCOVA) with baseline score as a covariate. If the post-treatment score was above the baseline score, the symptom score for that patient was judged as having shown improvement.

The *P* value for the primary analysis was presented one-sided in accordance with the trial design, while other values were two-sided. All analyses were carried out using SAS version 9.1 software (SAS, Cary, NC, USA).

Results

Figure 1 summarizes patient disposition in the trial. Enrollment into the study began in April 2003 and the study was terminated in April 2006. A total of 126 patients from 20 institutions in JCOG were enrolled and randomly assigned. All patients received study treatment; thus, all 126 patients were included in the safety analysis population. However, since one patient in the D group was ineligible due to prior radiotherapy for brain metastases within 2 weeks before accrual, that patient was excluded from the efficacy analyses.

Patient characteristics

Baseline characteristics of patients were similar in the two treatment groups as a whole except that more patients in the monotherapy group had cerebrovascular diseases and diabetes as comorbid diseases (Table 1). More patients with non-squamous histology were identified in the DP arm than in the D arm especially in the subgroup between 70 and 74 years old. Whereas the percentage of patients with Stage III without pleural effusion was larger in the D arm than in the DP arm in the subgroup between 70 and 74 years old. Diabetes was significantly more frequent in patients assigned to D arm than in those assigned to DP arm as a whole and in the subgroup between 70 and 74 years old.

Dose administration

Overall, 30 (47.6%) of 63 patients in the D arm and 40 (63.5%) of 63 patients in the DP arm received four or more cycles of chemotherapy. The median number of treatment cycles was 3.0 and 4.0 cycles, respectively (D range 1–8 cycles; DP range 1–7 cycles). The percentages of patients who received more than six cycles were 15.9% for D and 6.3% for DP arm. The major reasons for ending treatment in the D and DP arms were disease progression (68 and 41%, respectively), adverse events (13 and 19%, respectively) and patient refusal related to toxicity (11 and 32%, respectively). The toxicities that did not meet the criterion for stopping study treatment but led to study discontinuation were mostly ≤Grade 3 fatigue, anorexia, nausea and diarrhea. However, 40% of the patients who refused the treatment continuation for some reasons related to toxicity completed four or more cycles and 70% of them completed three or more cycles.

Efficacy

The second planned interim analysis was performed on 112 assessable patients (D/DP, $n = 56$ each; ≤74 years/≥75 years, 39/61%; male/female, 77/23%; III/IV, 30/70%) in March 2006. Information time, defined as the proportion of interim events to the planned events,

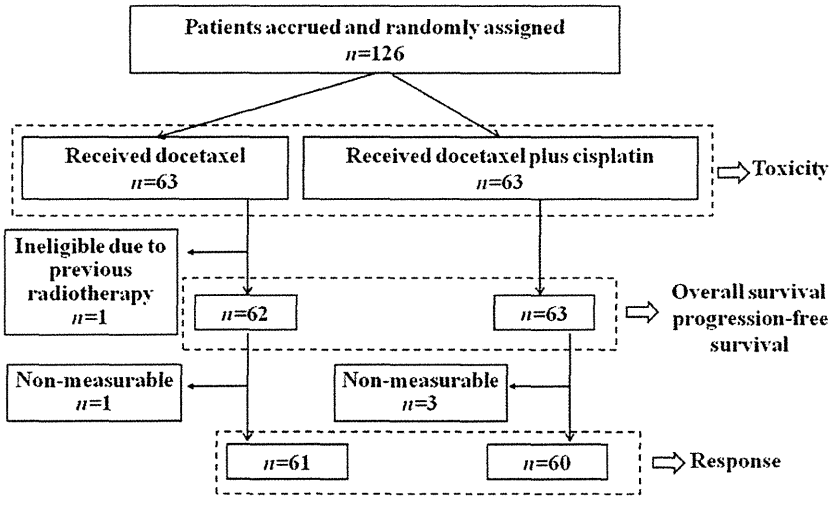

Figure 1. Patient disposition.

Table 1. Patient characteristics

	Docetaxel			Docetaxel + cisplatin		
Age, years	≤74	≥75	All	≤74	≥75	All
No. of patients	25	38	63	24	39	63
Characteristic						
Age, years						
Median	72	77	76	73	77	76
Range	70–74	75–88	70–88	70–74	75–86	70–86
Gender, *n* (%)						
Male	20 (80)	29 (76)	49 (78)	15 (62)	33 (85)	48 (76)
Female	5 (20)	9 (24)	14 (22)	9 (37)	6 (15)	15 (24)
Performance status, *n* (%)						
0	11 (44)	12 (32)	23 (37)	12 (50)	14 (36)	26 (41)
1	14 (56)	26 (68)	40 (63)	12 (50)	25 (64)	37 (59)
Disease stage, *n* (%)						
III	10 (40)	10 (26)	20 (32)	5 (21)	14 (36)	19 (30)
With pleural effusion	3 (12)	6 (16)	9 (14)	2 (8)	3 (8)	5 (8)
Without pleural effusion	7 (28)	4 (10)	11 (17)	3 (12)	11 (28)	14 (22)
IV	15 (60)	28 (74)	43 (68)	19 (79)	25 (64)	44 (70)
Histology, *n* (%)						
Squamous	11 (44)	14 (37)	25 (40)	5 (21)	13 (33)	18 (29)
Non-squamous	14 (56)	24 (63)	38 (60)	19 (79)	26 (67)	45 (71)
Weight loss, *n* (%)	5 (20)	11 (29)	16 (25)	6 (25)	11 (28)	17 (27)
Prior surgery, *n* (%)						
Primary lesion	2 (8)	0	2 (3)	1 (4)	6 (15)	7 (11)
Comorbid illness, *n* (%)						
Cardiovascular	1 (4)	2 (5)	3 (5)	2 (8)	2 (5)	4 (6)
Respiratory	3 (12)	4 (10)	7 (11)	3 (12)	4 (10)	7 (11)
Digestive/hepatic	0	2 (5)	2 (3)	2 (8)	2 (5)	4 (6)
Cerebrovascular	0	5 (13)	5 (8)	0	0	0
Diabetes	7 (28)	2 (5)	9 (14)	2 (8)	0	2 (3)

was 0.26 (49/191). As the one-sided *P* value ($P = 0.00515$) from the stratified log-rank test by age and stage was not lower than the multiplicity-adjusted bound of 0.0000096 for interim analyses, the formal criterion for suspending the trial was not met. However, subgroup analyses of age, one of the adjustment factors for randomization showed that OS was markedly worse in D than in DP (hazard ratio for DP over D, 0.23; 95% confidence interval (CI), 0.09–0.62) for the subgroup of 70–74 years old, although no significant difference between treatment arms was detected (hazard ratio, 0.72; 95%CI, 0.35–1.49) for patients ≥75 years old. The *P* value for interaction between subgroup by age and treatment arms was $P = 0.077$, indicating that D may be disadvantageous for the subgroup between 70 and 74 years old (Fig. 2). The Data and Safety Monitoring Committee (DSMC, one of the standing committees of JCOG, 20 members except for the investigators of this study participated the review) recommended study termination and disclosure of the results, although no rule to reach this decision had been pre-specified in the protocol. The final analysis was performed on 125 eligible patients in February 2007. Subgroup analyses of age in the final analyses also showed that OS was worse in D than in DP (hazard ratio for DP over D, 0.508; 95% CI, 0.259–0.997) for the subgroup of 70–74 years old, whereas no significant difference between treatment arms was detected (hazard ratio 0.822; 95%CI, 0.483–1.400) for patients ≥75 years old. However, the *P* value for interaction between subgroup by age and treatment arms became $P = 0.45$.

Overall response rates in 121 patients significantly favored DP (55.0%) over D (26.2%; $P = 0.0016$ by Fisher's exact test; Table 2). The difference was larger in patients 70–74 years old (DP, 69.6%; D, 16.7%) than in patients ≥75 years old (DP, 45.9%; D, 32.4%).

By 13 February 2007, a total of 91 (72.8%) of the 125 eligible patients had died (DP, $n = 45$; D, $n = 46$). For DP and D, median survival times was 17.0 months and 10.7 months and 1-year survival rates were 66.6 and 45.2%, respectively (two-sided $P = 0.0384$, log-rank test) (Fig. 3). The difference was larger in patients 70–74 years old (DP, 24.0 months, 78.9%; D, 9.9 months, 45.8%) than in patients ≥75 years old (DP, 13.6 months, 59.0%; D, 11.5 months, 44.7%) (Table 2). Median progression-free times for DP and D were 6.2 months and 3.7 months, and one-year PFS rates were 10.9 and 5.0%, respectively (two-sided $P = 0.0004$, log-rank test) (Fig. 3). The difference was on the contrary larger in patients ≥75 years old (DP, 6.2 months, 12.7%; D, 3.6 months, 5.3%) than in patients 70–74 years old (DP, 6.1 months, 8.3%; D, 4.1 months, 4.6%) (Table 2).

Toxicity

Grades 3 and 4 hematological and non-hematological events are summarized in Table 3. No Grade 4 hematological toxicity was encountered in either arm. Grade 4 hyponatremia occurred in only one patient receiving D. Overall toxicity in both treatment arms was generally mild and well-tolerated in elderly patients.

One patient developed treatment-related interstitial pneumonia after four cycles of DP; despite steroid treatment, the patient died from this toxicity on Day 102 after the last treatment.

Symptom score

Baseline symptom score data were available for all 126 patients. Symptom score data at 8 weeks later were missing in six surveys due to death, severe impairment of general condition or refusal to participate.

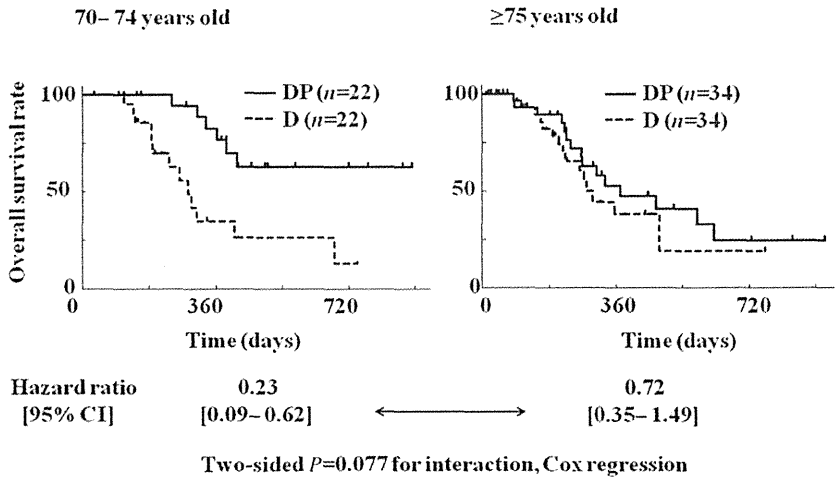

Figure 2. Overall survival by age subgroup at the second interim analysis. DP, docetaxel plus cisplatin; D, docetaxel; CI, confidence interval.

Table 2. Clinical efficacy data at final analysis

	Docetaxel			Docetaxel + cisplatin		
Age, years	≤74	≥75	All	≤74	≥75	All
No. of patients	24	37	61	23	37	60
Response						
Complete response	0	0	0	1	0	1
Partial response	4	12	16	15	17	32
Stable disease	13	8	21	6	12	18
Progressive disease	6	15	21	1	5	6
Not assessable	1	2	3	0	3	3
Overall response rate (%)	16.7	32.4	26.2	69.6	45.9	55.0
(95% CI)[a]			(20.0–47.5)			(52.5–80.1)
Progression-free survival (median, months)	4.1	3.6[b]	3.7[c]	6.1[d]	6.2[e]	6.2[f]
Overall survival (median, months)	9.9	11.5[b]	10.7[c]	24.0[d]	13.6[e]	17.0[f]

[a] $P = 0.0016$.
[b] $n = 38$.
[c] $n = 62$.
[d] $n = 24$.
[e] $n = 39$.
[f] $n = 63$.

Deterioration of symptom score from baseline was observed in both treatment arms; the least square mean scores at baseline and 8 weeks were 19.7 and 19.4 for D arm and 20.1 and 19.0 for DP arm. There was no significant difference between the treatment arms (two-sided, $P = 0.564$, ANCOVA with baseline score as a covariate).

Discussion

This randomized study was conducted based on promising response and survival data from a Japanese Phase II study (19). A weekly D schedule (24) was selected as a control regimen instead of the tri-weekly schedule widely used in our country to facilitate the interpretation of study results. In addition, a previous study comparing the two schedules of D for elderly patients with advanced NSCLC reported a trend toward longer survival using a weekly regimen (25). The tolerability profile particularly in terms of hematological toxicities, was also more favorable with the weekly regimen. Weekly D as a second-line treatment for advanced NSCLC has been shown to offer similar efficacy to the tri-weekly schedule, with significantly less febrile neutropenia in a meta-analysis of five randomized trials (26). A recently reported prospective trial compared D (38 mg/m^2, on Day 1 and 8, every 3 weeks) with vinorelbine (25 mg/m^2, on Day 1 and 8, every 3 weeks) in 130 NSCLC patients aged ≥65 years (27). Although this trial was closed prematurely because of low accrual, it suggested that weekly D could have an efficacy comparable with that of vinorelbine as first-line treatment in elderly patients with advanced NSCLC.

Weekly D was considered the most appropriate control regimen, but, no published data from Phase II studies with the same dose (25 mg/m^2) were available at the time of planning this study, so, we planned a first interim analysis to confirm that the dose of weekly D